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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/028,395	02/24/1998	DARWIN J. PROCKOP	9598-32	4622

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MORGAN, LEWIS & BOCKIUS LLP
1701 MARKET STREET
PHILADELPHIA, PA 19103-2921

EXAMINER
SCHNIZER, RICHARD A

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1635	33

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/028,395	Prockop
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Jun 3, 2002* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Jun 3, 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☒ Applicant's reply has overcome the following rejection(s):
None

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attached

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *19 and 20*

Claim(s) objected to: _____

Claim(s) rejected: *1-18*

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s) *28 and 32*.

10. ☐ Other: Note attached PTO-892

ADVISORY ACTION

The request for reconsideration has been thoroughly considered but does not place the application in condition for allowance.

At pages 3-6 of the response Applicant responds to the issue of whether or not the instant specification provides guidance with regard to the treatment of any specific disorder, i.e. whether or not the specification teaches how to treat Parkinson's or stroke or spinal cord damage by disclosing how many cells should be administered, to what site they should be administered, when they should be administered, and by what route they should be administered. Applicant asserts that the claimed invention is analogous to bone marrow transplantation which is well known and accepted in the art. The claimed invention is also said to be analogous to fetal neural tissue transplants for the treatment of Parkinson's disease. By comparison the instant invention is said to improve on fetal neural transplantation treatments because MSCs are more readily available, can be expanded in culture, and are not removed by immune responses even when human cells are transplanted directly into the rat brain. Applicant asserts that given the level of skill in these analogous arts, undue experimentation would not be required to practice the invention given the teachings of the specification.

In response, the Office reiterates the findings of the court in Genentech, Inc, v Novo Nordisk A/S. When the specification omits any specific starting material required to practice an

invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, methods of treating specific diseases are claimed, but the specification offers only general guidance in the context of treating virtually any disease of the central nervous system, including cancer. No specific guidance relevant to the treatment of Parkinson's, stroke, ischemia, or spinal cord injury is given, other than that MSCs should be delivered to the site of injury, and that the MSCs may be genetically modified. The number of cells administered, the time of administration, and the route of administration, cannot be considered to be minor details which can be omitted in the process of providing an enabling disclosure. This is particularly evident when considering documents relied upon by Applicant for support. With regard to the route of administration, both Chen (2001) and Li (2001) go beyond the teachings of the instant specification because Chen teaches **intravenous** delivery and Li teaches **intraarterial** delivery, whereas the specification fails to teach delivery of MSCs by any vascular route. Furthermore, Li teaches that intraarterial delivery of MSC is superior to intracerebral implantation, thus the

results obtained by Li are not representative of those obtainable with the claimed invention. See page 8, first sentence of third paragraph. With regard to the timing of delivery, Hofstetter et al (2002) show that immediate treatment of spinal cord injury with MSCs leads to no therapeutic effect, whereas a significant effect is seen only if cells are delivered after 7 days. The instant specification provides no teaching in this regard, yet it appears to be critical to the success of the technique.

Applicant asserts at page 6, first paragraph, that a skilled artisan would have appreciated that cells can be administered intravenously or intraarterially, and relies for support on Lu et al 2001. However, Lu was published 6 years after the effective filing date of the application, and cannot be considered to reflect the state of the art at the time of filing, for example, *in re Wright*, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993). Thus it is not clear that one of skill in the art would have attempted to deliver MSCs to neural tissue by intraarterial or intravenous administration, particularly in view of the specification which recommends direct administration to the CNS, e.g. by injection into the brain. See page 8, lines 25-28 and Example 7, especially page 49, lines 12-26. While the specification does teach an example of intravenous administration via the tail vein, the results resulting engraftment occurred primarily in marrow, spleen, bone, and lung, with only a trace of cells found in the brain. See page 34, lines 24-29, and Table 1 of US Patent 5,716,616 which presents these results in tabular form, indicating that on average marrow spleen, bone, and lung contained about 40-fold more MSCs than brain as a result of intravenous administration. It

is not clear that this would provide motivation to one of skill in the art to pursue intraarterial or intravenous administration as a means to practice the instant invention.

In the paragraph bridging pages 6 and 7 of the response, Applicant addresses the issue of whether or not the specification provides adequate guidance with regard to genetic modification of MSCs for the claimed methods of treatment, asserting that the identity of such genes is known to those of skill in the art and is not a critical element that must be taught by the specification. Applicant relies for support on During et al (1994), Mandel et al (1998), Schwarz et al (1999), Himes et al (2001), and Andsberg et al (2002). However as noted above, developments occurring after the filing date of an application are of no significance regarding what one skilled in the art believed as of that filing date. See for example, *in re Wright*, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993). During et al (1994) is the only cited reference published prior to the time of filing. During teaches the striatal delivery to a rat model of Parkinson's disease of herpes virus vectors encoding tyrosine hydroxylase. However, this publication elicited a response from Isacson (Science 269(5225): 856, 1995), who cautioned that the data were unconvincing, thereby providing evidence of the unpredictability in the art at the time of filing. Isacson points out that the treatment regimen of During can be expected to damage striatal neurons, resulting in a reduction in turning behavior in the rat model, and leading to invalid interpretation of experimental data. See page 856, column 1, second full paragraph. Isacson also teaches that it is unlikely that the number of tyrosine hydroxylase-positive neurons detected by During would be sufficient to cause a behavioral reduction, and goes on to point out that the viral delivery system

used by During is prone to down-regulation of expression when delivered *in vivo*. See paragraph bridging columns 1 and 2 on page 856. Isacson also questions the significance of the data due to the small number of animals used in the study. See the last sentence of the first full paragraph of column 2, page 856. Thus, at the time the invention was filed, the interpretation of the results of During was controversial, reflecting the uncertain state of the art. For this reason, the During reference does not support the position that it was routine or obvious at the time of the invention to use genes encoding tyrosine hydroxylase to genetical alter cells for the treatment of Parkinson's disease.

In the first full paragraph of page 7 of the response, Applicant argues that many of the issues discussed in the rejection pertaining to the therapeutic MSC transplantation have been resolved by post-filing reduction to practice following the teachings of the specification. Applicant's arguments at page 7 regarding the issue of graft rejection as raised in the Sanberg article are persuasive in view of the working example in which human cells engrafted in rat brains without apparent immune rejection, and in view of similar post-filing results (e.g. Schwarz (2001, and Azizzi (1998)).

Applicant's arguments in the paragraph bridging pages 7 and 8 regarding the predictability of treating by MSC transplantation diseases in which cells have died are not persuasive. Applicant argues that treatment of such diseases or disorders with MSCs is not unpredictable because transplanted MSCs can either differentiate into other cell types which can replace dead or damaged cells, or they can provide an environment that rejuvenates damaged or

dying neuronal cells. Applicant relies for support on Kopen (1999), Woodbury (2000), Ankeny (2001), and Hofstetter (2002).

Kopen (1999) injected MSCs into mouse lateral ventricles, showed that these cells migrated throughout the brain, and showed that some of the MSCs differentiated into astrocytes, and some may have differentiated into neurons. Woodbury (2000) extends the teachings of Kopen, and concludes that rat and human MSCs can be differentiated *in vitro* into cells that express a variety of markers typical of neurons. Although Woodbury teaches that these cells are in fact neurons, this conclusion is called into question by the teachings of Hofstetter et al (2002). Hofstetter teaches that these neuron-like cells lack voltage-gated ion channels necessary for the generation of action potential, and are not neurons. See abstract. In fact, Hofstetter teaches that several attempts were made to differentiate MSCs into neurons using a wide variety of differentiation factors, none of which were successful. See page 2204, column 1, lines 10-17. This provides evidence of the unpredictability associated with directing the fate of MSCs, and casts doubt on the proposition that MSCs can be differentiated into any neuronal cell other than an astrocyte. Similar to Hofstetter, Ankeny (2001) teaches that transplantation of MSCs into spinal cord-damaged rats, three days after injury resulted in therapeutic effect (air-stepping behavior) in 3 of 6 rats.

So, Applicant's argument depends on the results of Hofstetter (2002) and Ankeny (2001) which indicate that administration of MSCs after spinal cord injury can have a therapeutic effect. However, both of these references teach methods that are not disclosed in the instant

specification. Specifically, Hofstetter teaches that transplantation of MSCs immediately after injury led to no therapeutic effect, and that therapeutic effect depended on waiting seven days after injury before transplantation. See Fig. 3 on page 2201; and paragraph bridging pages 2201-2203. Ankeny teaches administration three days after injury. The instant specification provides no guidance or example that would lead one of skill in the art to delay transplantation to three or seven days after injury, yet the data of Hofstetter show that the method is inoperable if transplantation occurs immediately after injury. One of skill in the art, depending on the teachings of the specification and the prior art, would not have known that any delay in treatment was necessary in order to rejuvenate dead or dying cells, unless apprised of the results of Hofstetter which were not published until seven years after the effective filing date of the application. Therefore, the state of the art of treating with transplanted MSCs diseases and disorders in which neuronal cells were dead or dying was unpredictable at the time the invention was filed.

At pages 8-10 of the response, Applicant considers the significance of the Sabate reference. In the first full paragraph of page 8, Applicant argues that the issues raised in Sabate with regard to gene therapy are largely obviated by using unmodified MSCs, or MSCs genetically modified *ex vivo*. Applicant states that three of the five issues enumerated by Sabate only apply to the special case in which MSCs are modified to express a transgene. More specifically, at pages 9 and 10, Applicant addresses the issues of targeting of cells, vector production, and inflammation, as raised in the Sabate reference. Applicant's assertion that these issues are not

relevant to the instant invention is persuasive. However at pages 8 and 9 Applicant addresses the issues of extent and stability of transgene expression. Applicant argues that "the extent of transgene expression" is not a major concern because the cells may be assayed prior to implantation to confirm expression. Also, "the stability of transgene expression" is much less of a concern because the transgene can be introduced by self-inactivating viruses or by non viral means. Applicant relies on Schwarz (2001) and Keating (1990) for support. Applicant's dismissal of the issues of "the extent and stability of transgene expression" is unwarranted in view of the teachings of Schwarz (1999), who teaches that expression of transgenes in engrafted cells ceased by about 9 days after engraftment. See abstract. Although Schwarz (2001) teaches the use of self-inactivating viruses to provide transgene expression *in vitro* for nearly 4 months, (see page 1219, column 2, third full paragraph), the teachings that allow this result are not present in the specification, and are only disclosed six years after the effective filing date of the application. Keating indicates that use of the CMV promoter allows long-term stable gene expression in isolated stromal cells, but the cited abstract does not disclose how long expression lasted, nor whether it was maintained after transplantation in vivo. For these reasons, the teachings of Keating are insufficient to adequately support applicant's argument.

At page 10, second paragraph, Applicant argues that the specification need not disclose any known therapeutic gene in order to enable the scope of the invention embracing genetically modified cells, (e.g. claims 9 and 11 and dependents) wherein the genes were known at the time of filing and the importance of the genes in treating disease was appreciated at the time of filing.

This is unpersuasive because Applicant has failed to establish that known genes were routinely used to perform successful gene therapy at the time of filing. Unless gene therapy was practiced with routine success at the time of filing, the identity of a gene intended to produce a therapeutic product in a cell must be considered to be an essential feature of the invention. As noted above, the courts have found that the failure to disclose critical elements of an invention, whether or not they were known in the prior art, results in a failure to satisfy the enablement requirement. See Genentech, Inc, v Novo Nordisk A/S, 42 USPQ2d 1001.

On pages 10 and 11, Applicant revisits the issue of whether or not the instant claims are enabled by experiments in which transplanted MSC were used to treat osteogenesis imperfecta (OI), concluding that these experiments provide evidence that unmodified MSCs can be used to effectively treat disease in humans. In response, the Office reiterates that these experiments provide evidence that one can treat OI with MSCs. These experiments provide no evidence that one can treat any neurological disease or disorder with MSCs. As noted in Paper No. 12, pages 5 and 6, OI is caused by defects in a gene required for the synthesis and secretion of collagen. Applicant has presented no evidence that such defects cause any neurological disease or disorder. Further, Horwitz teaches that the collagen synthesis ceases in MSCs that have engrafted into brain. For these reasons, the fact that MSCs are useful in the treatment of OI, a disease that is totally unrelated to neurological disorders, provides no support for the enablement of the instant claims.

At pages 11 and 12 of the response, Applicant addresses the validity of the animal models used in the study of Parkinson's, spinal cord injury, ischemia, and stroke, noting that each of these models has been used to develop at least one drug which is now used successfully in humans. These arguments are persuasive, but are not sufficient to support the full enablement of the instant claims because, as discussed above and more fully below, the examples on which Applicant depends to show post-filing reduction to practice do not teach the method as claimed. Rather these publications invariably modify the teachings of the specification in ways that would not have been obvious to one of skill in the art at the time of the invention. For example, neither the specification nor the prior art of record provide any guidance or example that suggests that transplantation of MSCs to damaged spinal cords should be delayed by 3 or 7 days, and that immediate transplantation would have no beneficial effect, as demonstrated by Hofstetter (2002).

At pages 12-15 of the response, Applicant addresses the issue whether or not the publications submitted as evidence of post-filing reduction to practice actually practice the invention as claimed.

At page 12, paragraph 2, Applicant argues that it would not have been undue experimentation to modify the teachings of the specification such that MSCs were delivered intraarterially to stroke/ischemia victims, as taught by Li (2001). In response, the Office reiterates Li teaches that based upon the teachings of the specification and the prior art of record it would have been unpredictable at the time of filing as to whether or not the method of Li would have been successful. This owes to the factors discussed in the original enablement

rejections. For example, Prockop (1997) indicates that several different strategies were being pursued for therapeutic use of MSCs, and that a phase I clinical trial demonstrated that the systemic infusion of autologous MSCs appears to be well tolerated, but also notes that "Obviously, however, a number of fundamental questions about MSCs still need to be resolved before they can be used for safe and effective cell and gene therapy" (see page 74, middle column). It was clear that this issue remained unpredictable years after the invention was filed because Gerson (1999) asked the question "[i]s systemic infusion optimal or is infusion into a target organ required?" (see page 264, left column). Because the specification does not teach the method of Li, and because one of skill in the art could not have predicted its success at the time the invention was filed, the specification cannot be considered to be enabling of the method of Li.

In the third paragraph of page 12, Applicant argues that although Olson (2001) taught no therapeutic effect of MSC transplantation, Hofstetter (2002) does teach such an effect. The results of Hofstetter have been addressed above. Briefly, Hofstetter does not teach the method as disclosed in the specification. Hofstetter teaches that success of the method depended on a delay between the time of injury and the time of treatment. Due to the unpredictability in the art at, and after the time of filing, as evidenced by Prockop (1997) and Gerson (1999), and the failure of the specification to provide any guidance as to the timing of administration of MSCs relative to the time of spinal injury, one of skill in the art at the time of the invention could not have predicted

the success of the method of Hofstetter, nor foreseen the necessary modifications to the specification.

In the paragraph bridging pages 12 and 13, Applicant addresses the Examiner's concerns regarding the statistical significance of the data of Chen (2001), Li (2001), and Chopp(2000). In view of the fact that the authors assert that their results are significant, the Examiner accepts them as such. However, it is noted that each of these references modifies the teachings of the specification. Chen and Li teach intravenous and intraarterial delivery of MSCs, and Chopp teaches a delay of seven days after spinal injury before delivering MSCs. None of these modifications is enabled by the specification for the reasons discussed above, i.e. at the tie of filing the results of the claimed method were highly unpredictable, and the specification offers no guidance that would have led to the modifications reported in the post filing art.

At pages 13 and 14, Applicant addresses the enablement of methods requiring the delivery of differentiated MSCs. Applicant argues that Schwarz (1999) and Schwarz (2001) demonstrate the usefulness of partially differentiated cells for the treatment of Parkinson's Disease. This is unpersuasive because the it is not clear that these cells meet the definition of differentiated. Applicant appears to argue that because the cells were transfected with expression constructs leading to the secretion of L-DOPA that the cells are differentiated. The term "differentiated" in the context of the specification appears to mean that a cell has taken on the phenotypic characteristics of another cell type. See e.g. page 6, lines 24-29. While the secretion of L-DOPA is certainly a characteristic of another cell type, i.e. neurons, it is not clear that the

cells in either Schwarz publication are neurons. In fact, Hofstetter (2002) was unable to promote differentiation of MSCs into neurons despite repeated efforts. See page 2204, column 1, lines 10-17. For these reasons, the cells of Schwarz (1999) and Schwarz (2001) are not considered to be differentiated within the meaning of the specification.

At paragraph 1 of page 14 Applicant argues that Kopen demonstrates that differentiated MSCs can be used to treat CNS disease, especially where astrocytes and their factors provide a therapeutic benefit for treating disease. In response, the PTO notes that Kopen teaches the administration of nondifferentiated MSCs which subsequently migrate and differentiate into astrocytes. Neither Kopen nor the specification, separately or combined, provides sufficient guidance as to how to treat stroke, ischemia, Parkinson's, or spinal cord injury by transplantation of differentiated astrocytes. No guidance is given as to the number of astrocytes required or the timing or location of their transplantation relative to the time and site of injury.

At page 14, paragraph 2 Applicant argues that Hofstetter (2002) demonstrates that differentiated MSCs play a role in providing therapeutic benefit for treatment of Parkinson's, stroke and spinal cord injury. In response, the PTO notes that Hofstetter does not teach the administration of differentiated MSCs as required by the claimed methods, thus it is not clear that Hofstetter provides any support for these methods. Further, and as noted above, the specification provides no guidance or example that would lead one of skill in the art to delay transplantation to three or seven days after injury, yet the data of Hofstetter show that the method is inoperable if transplantation occurs immediately after injury. It is not clear from the teachings of Hofstetter,

exactly what type or types of cells were responsible for any therapeutic benefit. Were the astrocytes, sufficient, were the neuron-like cells, sufficient, or was the presence of both MSCs and differentiated MSCs required? One of skill in the art at the time the invention was filed would have no way to know, even armed with the post-filing teachings of Hofstetter. Therefore one of skill in the art, would not know what kind of differentiated cell to transplant in order to successfully treat spinal cord injury, or even that treatment of spinal cord injury was possible by transplantation of any differentiated cell.

In summary, the specification fails to provide an enabling disclosure because it fails to provide critical elements of the invention, such as the identity of therapeutic genes, and it fails to provide adequate guidance which is only provided in the post-filing art. The teachings of the post-filing art, relied upon by Applicant as reduction to practice, do not teach the invention as claimed, rather they teach modifications of the invention which one of skill in the art at the time of the invention could not have predicted would have resulted in success.

For these reasons the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit

1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER